Application Number 09/708,276

Please enter new claim 42:

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42. (new) The kit of claim 36, wherein the gene encoding p27 and the gene encoding the cytotoxic agent form a dicistronic construct.

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REMARKS

Claims 29 – 34 and 36 - 42 are pending. Favorable reconsideration and allowance is respectively requested.

Claim Amendments and New Claim

Applicant has amended claims 36, 39, and 40 and added new claim 42. No new matter has been introduced into this application by reason of the amendments and new claim presented herewith. The amendments to claims and new claim are supported by the following references to the Specification.

Claim 36 is amended to include the limitations of cancelled claim 35. Claims 39 and 40 are also amended to include the limitations of cancelled claim 35. The amendments to claims 36, 39 and 40 are supported by claim 35.

New claim 42 is supported by the Specification, page 15 lines 3 – 6 which describe a dicistronic construct expressing p27 and tk.

Disclosure Objections

The specification is objected to under 35 U.S.C. § 132 as allegedly introducing new matter at page 7, line 16 where the application was amended to read "therapeutically effective." The Applicants traverse this objection. The original specification, page 11,

lines 17 – 20, discloses the invention of a composition of "a therapeutically effective amount of a gene which expresses p27 and a pharmaceutically acceptable carrier." In addition, the original specification, page 12, lines 22 - 23 discloses that the invention may be used in the treatment of vascular proliferative diseases. In view of the above arguments, Applicants request reconsideration of this objection.

The Examiner objected to the Brief Description of the Figures as improper. The Applicant has amended the description of figures 2A-C, 3A-C, and 4A-C as requested by the Examiner. In addition, some typographical errors have been corrected. No new matter has been introduced in these amendments.

Claim Rejections Under 35 U.S.C. §102

Claims 29, and 32-35 stand rejected under 35 U.S.C. §102(e) as being anticipated by Fang, U.S. Patent Number 6,110,744 (the '744 patent). The Examiner alleges that the '744 patent taught a composition comprising a nucleic acid encoding p27 gene and a catheter. In addition, the nucleic acid is allegedly contained in an expression vector which may also comprise a second gene.

The Applicants enclose a declaration pursuant to 37 CFR §1.131 stating that they were in possession of the claimed collection of a nucleic acid encoding p27 and a catheter before the earliest effective filing date of the '744 patent. In view of this declaration, withdrawal of this rejection is requested.

Claims 29, 32-35, 39, and 40 stand rejected under 35 U.S.C. §102(e) as being anticipated by Gyuris, U.S. Patent Number 5,672,508 (the '508 patent). The Examiner alleges that the '508 patent taught a composition comprising a nucleic acid encoding p27

gene and a catheter. In addition, the nucleic acid is allegedly contained in an expression vector which may also comprise a second gene which may be a fusion protein (operably linked).

The Applicants respectfully submit that the complete subject matter of Claims 29, 32-35, 39, and 40 are not taught by the '508 patent. The '508 patent describes inhibitors of cyclin-dependent kinases (CDKs) that are made up of chimeric proteins comprising CDK-binding motifs from two or more different proteins. Chimeric proteins disclosed include those containing the CDK-binding motif of p16, p15, p21, p27, p57, or other proteins containing a CDK-binding motif (column 5, lines 18-20; column 5, lines 2-4). These chimeric proteins are said to have properties greater than the individual polypeptides that make up the chimeric proteins (column 4, lines 36-47). Because of this increased activity, the '508 patent suggests that these chimeric proteins may be useful in treating smooth muscle cell proliferation (column 14, line 41). However, nowhere is it taught that a kit comprising a catheter and a nucleic acid encoding p27 would be effective for the treatment of a vascular proliferative disease.

Even if, *pro arguendo*, the '508 patent were to suggest a kit comprising a catheter and a nucleic acid encoding a single CDK-binding motif effective for the treatment of a vascular proliferative disease, the '508 patent fails to teach which of the many proteins disclosed would be effective and which would not be effective. Indeed, throughout the '508 patent, p16 is discussed (column 2, line 43; column 4 lines 39-42; column 5, line 18 and line 26; column 7 line 67; column 21, line 36; and the exemplification section). If the '508 patent were to suggest that a protein containing only a single CDK-binding motif could be effective for the treatment of a vascular proliferative disease, one would assume

that p16 would be effective in such treatments. However, p16 is not effective for the treatment of vascular proliferative disease (Tanner *et al.*, "Gene Transfer of $p27^{KIP2}$ and $p21^{CIP1}$ Cyclin-Dependent Kinase Inhibitors, But Not $p16^{INK}$, Negatively Regulate VSMC Proliferation Through Differential Effects on Kinase Activity" Circulation Vol. 96(8): Suppl. p15 1997 – submitted in the Information Disclosure Statement filed January 22nd, 2001). Therefore, by failing to specifically point out which of the many proteins described therein would be effective in treating vascular proliferative disease, one skilled in the art, upon reading the '508 patent, is not guided to any specific protein as useful in its own right, no less to p27 alone. Simply describing a genus of compounds is not sufficient to satisfy the written description requirement as to a particular species or sub-genuses. Fujikawa v. Wattanasin 39 USPQ2d 1895, 1905 (1996). Given such a disclosure, one of ordinary skill would not be led to a particular compound. Id.

Furthermore, the cytotoxic agent described in amended claims 36, 39, and 40 does not contain a CDK-binding motif. Neither does the fusion protein described in claim 40 contain more than one CDK-binding motif. Therefore, the '508 patent is not anticipatory of amended claims 39 and 40. Withdrawal of the §102(e) rejection is requested for the reasons stated above.

Rejections under 35 U.S.C. §103(a)

Claims 29-35, 39 and 40 stand rejected under 35 U.S.C. §103(a) as being unpatentable over the '744 or '508 patents, each in view of U.S. Patent Number 5,328,470 (the '470 patent). Allegedly, the '470 patent taught a single and a double

balloon catheter for the direct delivery of recombinant nucleic acids encoding genes to the walls of blood vessels.

Applicants have submitted a declaration pursuant to 37 CFR §1.131 stating that they were in possession of the claimed collection of a nucleic acid encoding p27 and a catheter before the priority date of the '744 patent. In addition, as shown above, Applicants have removed the '744 patent as a reference and addressed the '508 patent above. The '470 patent does not teach a kit comprising a catheter and a nucleic acid encoding p27 and, hence, does not make up for the deficiencies of the '744 and '508 patents. Withdrawal of the §103 rejection is requested for the reasons stated above.

Claims 29-41 stand rejected under 35 U.S.C. §103(a) as being unpatentable over the '744 or '508 patents each in view of the '470 patent, and further in view of U.S. Patent Number 6,218,372 (the '372 patent).

Allegedly, the '372 patent taught a nucleic acid encoding a p21 gene and a balloon catheter where the p21 gene was operatively linked to a cytotoxic thymidine kinase gene or cytosine deaminase gene, which may be fusion proteins, where the nucleic acid may be a viral expression vector in a liposome, in a method of treatment of restenosis. The Examiner alleges that the above combination renders claims 29-41 obvious because each of the '744 and '508 patents taught that p27 may be used as an equivalent for p21 in a method of treatment of restenosis.

Applicants have submitted a declaration pursuant to 37 CFR §1.131 stating that they were in possession of the claimed collection of a nucleic acid encoding p27 and a catheter before the publication date of the '744 patent. In addition, Applicants have addressed the '508 patent above.

Applicants include herewith a statement indicating that the subject matter of the present application and the '372 patent was, at the time the invention of the present application was made, owned by the Trustees of the University of Michigan or subject to an obligation of assign to the Trustees of the University of Michigan. Hence, the '372 patent is not available as prior art. Accordingly, this rejection is rendered moot. Withdrawal of the §103 rejection is requested for the reasons stated above.

In reply to the Office Action dated March 19th, 2002, favorable reconsideration and allowance of this application are requested for the reasons set forth in the above remarks. If, for any reason, the Examiner is unable to allow the application on the next Office Action and feels that an interview would be helpful to resolve any remaining issues, he is respectfully requested to contact the undersigned attorney at (312) 321-4229.

Respectfully submitted,

Dated: August 27th, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE.

IN THE SPECIFICATION

Figures 2A-C. Figure [Figures] 2A is a schematic representation of the constructs expressing p27 and TK. Figure 2B is a histogram demonstrating the DNA profile of 293 cells transfected with the above-described plasmids and a CD2-expressing plasmid. All the CD-2 expressing cells are [ere] included in the analysis. The fraction of cells in each phase of the cell cycle is indicated above the corresponding peak. The percentages of CD-2-positive cells are [ware] indicated in the upper right corner of each graph to illustrate the variability in transfection efficiency. [Fig.] Figure 2C is a graph [histogram] showing the growth of 293 cells transfected with the above-described plasmids in the presence or in the absence of 5 μM GCV. Proliferation was measured using a colorimetric assay. Data is the average of 3 measurements.

Figures 3 A-C Figure 3A is a schematic representation of the constructs expressing p27 and TK. [Fig.] Figure 3B is a histogram demonstrating the DNA profile of 293 cells transfected with the above-described plasmids and a CD2-expressing plasmid. The fraction of cells in G1 phase of the cell cycle is indicated above the corresponding peak. The percentages of CD-2-positive cells are [ware] indicated the upper right corner of each graph to illustrate the variability in transfection efficiency. All values are the average of two experiments. Fig. 3C [Figure 2C] demonstrates the bystander assay. Renca cells were transfected with the various plasmids and diluted with untransfected cells. Addition of 5 μM GCV to the culture medium and cell proliferation assay were performed 1 and 5 days post-transfection, respectively.

Figures 4 A –C. Figure 4A is a histogram showing that mutation of the cdc2 kinase consensus site TRKK into GGAA moderately increase p27 activity. [Fig.] Figure 4B is a histogram showing the internal deletions inside the p27 coding region increase p27 activity. [Fig.] Figure 4C shows that fusion of the N-terminal domains of p21 and p27 does not increase cell cycle arrest in G1. All experiments were preformed using 293 cells as in [Figs.] Figures 2B and 3B.

IN THE CLAIMS

36. (Amended) The kit of claim [35, wherein the second gene encodes a cytotoxic agent] 29, wherein the nucleic acid further comprises a gene encoding a cytotoxic agent.

39. (Amended) The kit of claim [35] 36, wherein the gene encoding p27 and the [second] gene encoding the cytotoxic agent are operatively linked.

40. (Amended) The kit of claim 39, wherein the gene encoding p27 and the [second] gene encoding the cytotoxic agent are operatively linked such that they form a fusion protein.

42. (new) The kit of claim 36, wherein the gene encoding p27 and the gene encoding the cytotoxic agent form a dicistronic construct.

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EVIDENCE TO ESTABLISH COMMON OWNERSHIP

The subject matter of the present application and the subject matter of United States Patent Number 6,218,372 were, at the time the invention of the present application was made, owned by the Trustees of the University of Michigan or subject to an obligation of assign to the Trustees of the University of Michigan.

Respectfully submitted,

Dated: August 27th, 2002.

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